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10/563,271	01/04/2006	Hui-Fang Chang	101151-1P US	6300

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EXAMINER	
OLSON, ERIC	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,271	CHANG ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *August 28, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/GB04/02904, filed July 6, 2004, which claims benefit of provisional application 60/485523, filed July 8, 2003. Claims 1-26 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted January 4, 2006 is acknowledged wherein claims 2, 3, 5, 10, and 18 are amended and claims 27-29 are cancelled, and the specification is amended to indicate continuity and correct minor typographical errors.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-20 and 23-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, for failing to comply with the enablement requirement. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. "Prevention" as discussed herein is interpreted to mean the complete blocking of all symptoms or effects of a disorder for an indefinite period of time.

Nature of the invention: The claimed invention is drawn to a therapeutic method for treatment, prevention, or prophylaxis of a disorder. According to Merriam-Webster's Collegiate Dictionary, Tenth Edition, the word "prevent" is defined as, "to deprive of power or hope of acting or succeeding; to keep from happening or existing." The word "prophylactic," is defined as "guarding from or **preventing** disease," and the word "prophylaxis," is defined as, "measures designed to preserve health and **prevent** the spread of disease." In order for a preventative method to truly deprive a condition of power or hope of acting or succeeding, the treatment must be 100% successful at avoiding any occurrence of said condition at any time in the future.

The state of the prior art: The nicotinic acetylcholine receptor is known in the prior art to be involved in certain neurological disorders such as for example Alzheimer's disease. Ligands to this receptor have been used as therapeutic agents. These ligands are not known to be useful as preventative or prophylactic agents in the sense being used herein. In general, prevention of any disorder in the sense being used herein is not a recognized clinical outcome in the art, as no treatment is perfectly effective.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Prevention of a disease is not the same as treatment of said disease. In order to prevent a disease, as opposed to merely delaying or reducing its symptoms, a treatment must either render the subject completely resistant to said disease after a single treatment or a limited number of treatments, or else, when continued indefinitely, continue to completely suppress the occurrence of said disease. In order to practice a preventative method, one of skill in the art must know the answer to several questions in addition to the effectiveness of the therapy in short-term relief of symptoms, including:

1) What is the duration of a single course of therapy? How often must the therapy be administered to completely suppress the disease?

2) Does the subject develop tolerance to the therapy over time? Does the disease eventually progress to a point where the therapy is unable to completely suppress all symptoms? For example, will a metastatic cancer eventually adapt to overcome treatments directed to preventing it from metastasizing into the bone? Or will a case of osteoporosis or rheumatoid arthritis ultimately progress to a point where symptoms develop regardless of which therapy is administered.

3) What are the long-term effects of the therapy? Does it cause progressive damage to the kidneys, liver, or other organs? Does the active agent accumulate in the subject's tissues? Is the minimum dose necessary to completely prevent the disease safe for long-term administration? Are there any steps that can be taken to reduce side effects?

For this reason, many therapies which are suitable for short-term relief of symptoms are not suitable for lifelong prevention of disease. For example, antibiotics, chemotherapeutics, and antiviral drugs are not normally administered to healthy subjects in order to prevent the development of infection or cancer.

The Breadth of the claims: In the absence of an explicit definition in Applicant's specification, the claims are given their broadest reasonable interpretation. See MPEP 2111. As discussed above, prevention in the sense used herein must be capable of stopping any occurrence of a condition at any time in the future. Merely slowing the onset of disease or making the disease less likely would still leave it with "power or hope of acting or succeeding," and thus not qualify as prevention.

The amount of direction or guidance presented: The claimed compounds are shown to be ligands for the nicotinic acetylcholine receptor, which suggests a **therapeutic** utility. No guidance is given in the specification suggesting any reason to believe that the claimed compounds are uniquely useful as preventative agents.

The presence or absence of working examples: No working examples for the prevention or prophylaxis of disease are provided.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: As mentioned above, the short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness for prevention of disease. Because no guidance is given for the use of the

claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so without first gathering information as to the long-term effectiveness of the therapy. In particular, one skilled in the art, in order to practice the invention for prevention of disease, would need to know whether the preventative effect remains potent over the long term.

In order to answer these questions in the absence of any existing data, one skilled in the art, in order to practice the invention, would undertake long-term animal tests, preferably over a period of years, preferably involving a relatively long-lived experimental animal such as dogs or monkeys, or a human clinical trial. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Administering the claimed compounds for a period of years to a suitable subject population is an undue amount of experimentation needed in order to practice the full range of the claimed invention. As prevention in the full sense is an extremely high bar for any clinical outcome, there is no reason to believe that the therapy would be successful, and any actual success would be a surprising and unpredictable result.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the nature of the invention, Applicants fail to provide information sufficient to practice the claimed invention for the prevention or prophylaxis of a disorder associated with the nicotinic acetylcholine receptor.

Claims 18-26 are rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the enablement requirement. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating a "human disease or condition in which activation of the α7 nicotinic receptor is beneficial." In order to practice a method for a broad class of embodiments, one skilled in the art must

be able to reasonably and exhaustively define which disorders are included within the claim limitations.

The state of the prior art: Nicotinic acetylcholine receptors are suspected to be involved in certain neurological disorders such as for example Alzheimer's disease. However, there are multiple subtypes of this receptor, with differing biological activities. According to Holladay et al. (Reference included with PTO-892) the role of the α7 nicotinic acetylcholine receptor is still under investigation. Therefore it is not known what if any disorders can be treated by agonists of this receptor. Furthermore, the prior art does not exhaustively disclose a complete explanation of the causes of every neurological disorder, in such a way as to reveal to one skilled in the art all disorders affected by said receptor.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The study of neurological disorders is highly unpredictable. One skilled in the art would not know for certain the full range of neurological and psychiatric effects of α7 nicotinic receptor activation, or the exact biochemical causes of each and every neurological disorder. Often, neurological disorders are known by symptoms (e.g. psychosis, intellectual impairment) rather than as being related to a specific biochemical cause.

The Breadth of the claims: The claimed invention is very broad, including any disorder that can be improved by activation of a particular receptor. Dependent claims 19 and 25 limit the claimed disorders to neurological disorders, psychotic disorders, and intellectual impairment disorders. Neurological disorders include any disorder related to

the physiological function of the brain. Psychotic and intellectual impairment disorders are defined by certain general types of symptoms without regard to the underlying symptoms, if such are even known.

While members of a particular class of receptors share certain similarities, there is no expectation that they will produce the same biological effects or be useful for treating the same disorders. It is highly unpredictable which members of a receptor family will be useful for treating which disorders.

The amount of direction or guidance presented: The only direction or guidance presented is the indication that the claimed compounds activate the α7 nicotinic receptor, and are thus expected to possess similar utility to prior art compounds that activate the same receptor. However, the prior art does not actually provide enabling disclosure of therapeutic methods using similar compounds. No new information as to the therapeutic utility of this class of receptor ligands is provided.

The presence or absence of working examples: No working examples are given for the treatment of any disorder whatsoever.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the treatment of broad classes of neurological disorders. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would need to know which disorders are in fact treatable by the claimed method. Because of the incomplete knowledge in the art and the lack of further guidance or examples from Applicant's specification, one skilled in the art would

have to independently determine the full scope of disorders that can be treated by the disclosed therapy. In fact there is no conclusive reason to believe that these compounds can be used to treat any disorders. Finding clinical indications for these compounds would require extensive investigation, both theoretical and experimental, of numerous neurological and psychological disorders, as well as the biochemical systems involved, and would require further research on the biological function of the α7 receptor. Such original experimentation is neither routine nor predictable, and therefore constitutes an undue burden of unpredictable research.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance or working examples, Applicants fail to provide information sufficient to treat a disorder with an agonist of the α7 nicotinic receptor.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katayama et al. (PCT international publication WO01/66546, reference included with PTO-1449) Katayama et al. discloses a formula (I) which, when m=n=2, R1=H, and X=Y=O, encompasses a broad class of compounds in which the group Ar is a substituted phenyl groups. It is noted that for all embodiments of the claimed invention the group Ar1-A-Ar2 falls within the definition of "substituted phenyl" when Ar1 is phenyl. Katayama et al. does not teach the specific substituents –A-Ar2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make and test various embodiments of the generic structure of Katayama et al. as potential therapeutic agents. One of ordinary skill in the art would have done so in order to explore the possible therapeutic applications of specific embodiments of the generic structure of Katayama et al.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katayama et al. as applied to claims 1-14 above, and further in view of Holladay et al. (Reference included with PTO-892) in view of Bylund et al. (Reference included with PTO-892) The disclosure of Katayama et al. is discussed above. Katayama et al. does not disclose tritiated compounds or a method of assaying specific compounds for binding to the α7 nicotinic acetylcholine receptor.

Holladay et al. discloses that nicotinic acetylcholine receptors are promising therapeutic targets for a number of diseases. (p. 4169, right column, paragraphs 1-

2)The role of the α7 nicotinic acetylcholine receptor is still under investigation. (p. 4173, left column, fifth paragraph)

Bylund et al. discloses a review of various techniques for measuring ligand binding using radioisotopes. (p. 2897, first paragraph – 2898, fourth paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to make tritiated derivatives of the compounds of Katayama et al. and to use these tritiated compounds in ligand binding assays according to instant claim 17. One of ordinary skill in the art would have modified the invention in this manner in order to study the binding affinities of different compounds of instant claim 1 in order to evaluate them as potential therapeutic agents.

Thus the invention taken as a whole is *prima facie* obvious.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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